This objection is overcome by the submission of a SUPPLEMENTAL DECLARATION/POWER OF ATTORNEY FOR UTILITY PATENT APPLICATION under 37 C.F.R. §1 .67(c) executed by Jeffrey S. Glenn.

Claim objections

Claims 13-21 are objected to because they lack proper introduction.

This objection is overcome by the insertion of "I claim" before claim 13.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 13-21 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner alleges that the instant disclosure fails to enable the invention of claims 13-21 for the following reasons.

Rejection based on Benet and Rice

The Examiner states that the art teaches that the efficacy of therapeutics is dependent upon factors such as solubility of the drug, bioavailability at the target site, attainment of effective plasma concentrations, solubility in tissues, biotransformation, toxicity, rate of excretion or clearance, and in the case of antivirals, propensity for emergence of resistant strains (citing Benet et al., pp. 3-32, in The Pharmacological Basis of Therapeutics, 8th ed., 1990). The Examiner also states that the art further teaches that "the story of drug discovery for viral diseases is replete with failures" and that drugs which are quite effective in the laboratory often reveal disappointing traits in the clinical setting (Citing Rice et al., Advances in Pharmacology 33:389-438, 1995).

This rejection is respectfully traversed for the following reasons. First, it seems that the Examiner's concerns based on Benet, *i.e.*, solubility of the drug, bioavailability at the target site, attainment of effective plasma concentrations, solubility in tissues, biotransformation, toxicity, rate of excretion or clearance, are not related to enablement of the presently claimed method. Rather, these questions, in essence, relate to efficacy and toxicity of anti-prenylation treatment. However, as the Board in Ex parte Balzarini stated, these concerns and questions are to be dealt

with appropriate medical regulating authorities and/or the treating physicians. Ex parte Balzarini, 21 USPQ2d 1892, 1895 n.3 (Bd. Pat. App. & Int'f 1991) (regarding utility of composition and method for treating retroviral diseases or "HIV" in human cells"; "We do not find the examiner's concern in regard to possible side effects occurring from treatment of AIDS patients with other anti-viral drugs to be particularly relevant to the present inquiry since the occurrence of side effects does not raise the issue of whether the anti-viral drug in and of itself exhibits in vivo anti-viral activity. Whether such side effects outweigh the anti-viral utility in treating specific patients suffering from specific diseases is a matter left to the appropriate medical regulating authorities and/or the treating physician").

In addition, many of the Examiner's concerns, especially the concern on the toxicity or lack of specificity of the claimed anti-prenylation treatment, have been considered and dealt with by the skilled artisans. For example, following the teachings of the present application, Glenn et al., *J. Virol.*, 72(11):9303-6 (1998)) (Exhibit B), established a cell culture model which produces HDV-like particles, and show that delta antigen prenylation can be pharmacologically inhibited by the prenylation inhibitor BZA-5B. BZA-5B specifically abolishes particle production in a dose-dependent manner demonstrating that the use of such a prenylation inhibitor-based antiviral therapy may be feasible and identify a novel class of potential antiviral agents. At page 9305, in the paragraph adjourning the left and the right columns, Glenn et al. also state that:

> Normal cellular prenylation is accomplished by a family of prenyltransferases. Thus, selective inhibition of the prenyltransferase that modifies delta antigen may not affect host cell functions which depend on other prenyltransferases. Some substrates can be prenylated by more than one prenyltransferase. Such potential cross-specificity may help mitigate unwanted prenylation inhibition of critical cellular proteins by BZA-5B. Indeed, BZA-5B is surprisingly well tolerated in a variety of experimental systems; in our experiments, we observed no gross cellular toxicity and a mild (30 to 50%) inhibition of growth rate at the highest BZA-5B concentrations. In addition, viral assembly may be more sensitive than key host cell functions to the effects of prenylation inhibitors. It is possible that inhibiting the prenylation of only a fraction of the large delta antigen in a nascent virus particle may be sufficient for abrogating normal assembly of the entire particle.

The selective inhibition of viral prenylation without affecting vital cellular function has been shown in the experiment described in the paragraphs 9-12 of the GLENN DECLARATION (Exhibit A). In that experiment, the inventor of the present application demonstrates that FTI-277, a prenylation inhibitor, can effectively inhibit the production of HDV virions at a

concentration that does not significantly affect general protein synthesis and secretion, and does not significantly affect overall cell metabolism.

Further, Rice is quite irrelevant to the presently claimed method. Rice reviews discovery and *in vitro* development of AIDS antiviral drugs as biopharmaceuticals. In Table 1, Rice lists the virus specific targets, including env, reverse transcriptase, RNase H, integrase, tat, p7NC zinc finger, protease, and cell specific targets, including CD4, ribonucleotide reductase, topoisomerase, O_2 intermediates/NF-kB, protein kinase C, glycosylase and cyclophilins, as well as inhibitory compounds for these targets (See Rice at page 398). None of the target/inhibitory compound involves inhibition of prenylation of a viral protein. Therefore, Rice has little, if any, bearing on the enablement of the presently claimed method which is based on the inhibition of prenylation of a viral protein.

Tetrapeptides that are CXXX box analogs

The Examiner states that the disclosure teaches that agents which inhibit viral protein prenylation encompass tetrapeptides that are CXXX box analogs. The Examiner alleges that the art teaches that the effectiveness of agents which inhibit protein prenylation *in vitro* is unpredictable when they are administered *in vivo*. The Examiner also states that adequate concentrations of the biologically active inhibitor must be maintained long enough to exert the desired effect on target cells and the agent must be able to penetrate tissues, target the infected cells, and be taken up by the cells. Specifically, the Examiner cites Gibbs for the proposition that FPP prevents cell penetration and the cellular uptake of tetrapeptide inhibitors is very inefficient and it may require significant modification before they are pharmacologically useful.

Again, it seems that these concerns are related to efficacy and toxicity of tetrapeptides that are CXXX box analogs and are not related to the enablement of the use of tetrapeptides that are CXXX box analogs for inhibiting viral protein prenylation. Gibb's comments that tetrapeptide inhibitors "may require significant modification before they are pharmacologically useful" does not mean that the use of these tetrapeptide inhibitors are not enabled. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. United States v. Telectronics, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). The test is not without any experimentation. Indeed, a patent need not teach, and preferably omits, what

is well known in the art. Spectra-Physics, Inc. v. Coherent , Inc., 3 USPQ2d 1737 (Fed. Cir. 1987). Techniques for developing therapeutics from lead compound are well known in the art and are taught in many textbooks, including the one cited by the Examiner, *i.e.*, Goodman and Gilman's The Pharmacological Basis of therapeutics. Following these commonly known techniques, peptide based protein prenylation inhibitors that are suitable for *in vivo* use have been developed (*See e.g.*, Exhibit J, O'Connor et al., *J. Med. Chem.*, 42:3701-3710 (1999), which discloses second-generation peptidomimetic inhibitors of protein farnesyltransferase demonstrating improved cellular potency and significant *in vivo* efficacy; and Exhibit K, Gu et al., *Eur. J. Cancer*, 35(9):1394-401 (1999), which discloses A-170634, a CAAX peptidomimetic farnesyltransferase inhibitor that has efficacy *in vitro* and *in vivo*).

Specificity of protein prenylation inhibition

Citing Hoffman, the Examiner asserts that the art teaches that protein prenylation inhibitors may result in a nonspecific shutdown of protein prenylation in general. Citing Rightsel and Detroy, the Examiner asserts that the art also teaches that inhibitors of viral protein prenylation may be insufficiently soluble for effective *in vivo* use and may be unacceptably toxic and/or carcinogenic.

Hoffman's comment that protein prenylation inhibitors may result in a nonspecific shutdown of protein prenylation in general is mere speculation without any experimental support. In contrast, the present Applicant has demonstrated that BZA-5B and FTI-277, both are prenylation inhibitors, can effectively inhibit the production of HDV virions at a concentration that does not significantly affect general protein synthesis and secretion, and does not significantly affect overall cell metabolism. As discussed above, specific inhibition of viral protein prenylation is possible because normal cellular prenylation is accomplished by a family of prenyltransferases and thus, selective inhibition of the prenyltransferase that modifies delta antigen may not affect host cell functions which depend on other prenyltransferases. In addition, viral assembly may be more sensitive than key host cell functions to the effects of prenylation inhibitors. Rightsel and Detroy's teaching is irrelevant here because neither Rightsel nor Detroy discloses or teaches treating viral infection by inhibiting viral protein prenylation inhibition.

Disclosure of the present application

The Examiner states that in light of the extensive teachings of unpredictability found in the art, the specification must contain sufficient guidance as to how to maintain adequate concentrations of biologically active inhibitors *in vivo,* how to target and penetrate virus-infected cells, how to achieve inhibition of viral protein prenylation in the absence of a general shutdown of protein prenylation, and how to achieve a therapeutically effective concentration without significant toxicity. The Examiner alleges that these teachings are absent from the disclosure. The Examiner also alleges that there is no guidance provided for overcoming the unpredictability found in the art regarding *in vivo* administration of antiviral therapeutics in general and the claimed agents in particular. The Examiner further alleges that there are no working examples describing *in vivo* administration of the claimed agents for treatment of viral infections. The Examiner concludes that in light of the absence of such guidance in the instant specification, it would require undue experimentation by one of skill in the art to practice the claimed invention.

This rejection is respectfully traversed for the following reasons. First, the present specification teaches how the inhibitors may be administered (See page 14, line 13 through page 15, line 19 of the present specification). For example, the present specification teaches that suitable formulations can be obtained by following the teachings from Remington's Pharmaceutical Sciences, a well recognized authority in the art. By deciding suitable formulations, the Examiner's concerns such as how to maintain adequate concentrations of biologically active inhibitors *in vivo,* how to target and penetrate virus-infected cells, and how to achieve a therapeutically effective concentration without significant toxicity, are necessarily considered. In addition, as discussed above, these concerns are mostly related to efficacy and toxicity of anti-prenylation treatment, which are to be dealt with appropriate medical regulating authorities and/or the treating physicians. Further, the alleged lack of working example here is not dispositive to the enablement issue because the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 164 USPQ 642 (CCPA 1970). Indeed, how a teaching is set forth, by specific example or broad terminology, is not important. In re Marzocchi, 169 USPQ 367 (CCPA 1971). The fact is that following the teachings of the present application, coupled with the knowledge known in the art, Applicant and

other skilled artisans have successfully developed various prenylation inhibitors that are suitable for *in vitro* and *in vivo* uses (See Exhibits A-B and H-I).

Prenyl group mimics

The Examiner alleges that the instant specification fails to enable the embodiment drawn to administration of an mimic of a prenyl group for the following additional reasons. The Examiner states that the disclosure fails to teach what is encompassed within mimics of the groups. The Examiner also states that the disclosure fails to provide guidance as to how these mimics can be made or administered. The Examiner further states that there are no teachings that these mimics actually inhibit viral replication either *in vitro or in vivo* and there are no working examples describing inhibition of protein prenylation by prenyl group mimics. The Examiner concludes that absent these teachings, it would require undue experimentation by one of skill in the art to discover these prenyl group mimics and to then determine which, if any, of the mimics would inhibit protein prenylation sufficiently to treat a viral infection in a subject.

This rejection is respectfully traversed. As discussed in connection with the parent application, the meaning of "mimic" is well known in the art. The dictionary meaning of "mimic" is to copy or imitate closely or to resemble closely (see Exhibit L: the American Heritage College Dictionary (3rd Ed.), Houghton Mifflin Company, Boston and New York, 1997, p866). Accordingly, "a mimic of a prenyl group" should behave like a prenyl group, *e.g.*, farnesyl diphosphate, but cannot be used as a prenyl group donor in a functional prenylation reaction. In one aspect, "a mimic of a prenyl group" can behave as a competitive inhibitor of a prenyl group donor in a prenylation reaction. Such a competitive inhibitor is disclosed in the submitted Pompliano article. Pompliano et al. showed that two nonhydrolyzable analogues of farnesyl diphosphate, (alpha-hydroxyfarnesyl)phosphonic acid (1) and [[(farnesylmethyl)hydroxyphosphinyl]methyl]phosphonic acid (2), are competitive inhibitors of farnesyl diphosphate and noncompetitive inhibitors of Ras-CVLS (Exhibit M, Pompliano et al., *Biochemistry*, 31:3800-3807 (1992)). This point is specifically taught at page 3804, in the paragraph adjourning the left and right columns of Pompliano, wherein it is disclosed:

> Reciprocal plots of initial velocities with respect to the concentration of farnesyl diphosphate in the presence of nonsaturating levels of Ras-CVLS at different fixed concentrations of 1 intersected on the 1/v axis, suggesting that 1 behaves as a competitive

inhibitor with respect to farnesyl diphosphate. Reciprocal plots of initial velocities with respect to the concentration of Ras-CVLS in the presence of nonsaturating levels of farnesyl diphosphate at different fixed levels of 1 intersected on the 1/[s] axis, indicating that 1 is a noncompetitive inhibitor of Ras-CVLS. Compound 2 showed the same competitive and noncompetitive behavior against farnesyl diphosphate and Ras-CVLS, respectively (emphases added)..

However, it should be noted that the above description of a mimic of a prenyl group behaving as a competitive inhibitor in a prenylation reaction is for illustration only. The meaning of the mimic of a prenyl group should not be limited to such competitive inhibitor because the mimic may block the normal prenylation through other mechanism(s). For example, a prenyl group may be modified so that, although it can be used as a prenyl group donor to be transferred to a CXXX box, the modification interferes with the function of the prenyl group, *e.g.*, blocking binding of the modified prenyl group with its receptor. In this way, the modified prenyl group can be used a mimic of the prenyl group because the modified prenyl group blocks functional prenylation of a viral protein with the CXXX box.

In addition, other examples of prenyl group mimics are well known in the art. Such exemplary prenyl group mimics include oreganic acid (Exhibit F, Silverman et al., *Biochem. Biophys. Res. Commun.*, 232(2):478-81 (1997)), 2-diazo-3,3,3-trifluoropropionyloxy-farnesyl diphosphate (DATFP-FPP) (Exhibit C, Bukhtiyarov et al., *J. Biol. Chem.*, 270(32):19035-40 (1995)), 1-phosphono-(E,E,E)-geranylgeraniol, a dead-end inhibitor for GGPP (Exhibit G, Stirtan and Poulter, *Biochemistry*, 36(15):4552-7 (1997)), Cbz-His-Tyr-Ser(OBn)TrpNH2 and Cbz-HisTyr(OPO42-)-Ser(OBn)TrpNH2 (Exhibit E, Scholten et al., *J. Biol. Chem.*, 272(29):18077-81 (1997)) and alpha-cyanocinnamide derivatives (Exhibit D, Poradosu et al., *Bioorg. Med. Chem.*, 7(8):1727-36 (1999)). It is noteworthy that these prenyl group mimics are molecules with distinct structures. Therefore, the term "prenyl group mimics" means, to those skilled in the art, not just a single group, but a diverse group of molecules.

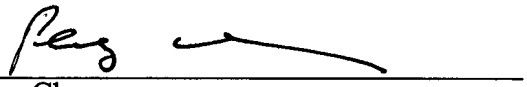
It is respectfully submitted that the rejection of claims 13-21 under 35 U.S.C. § 112, first paragraph, is overcome by the above remarks and must be withdrawn.

CONCLUSION

Applicant appreciates the recognition that claims 13-21 are free of arts. Applicant submits that the rejection of claims 13-21 under 35 U.S.C. §112 has been overcome by the above remarks. Early allowance of the pending claims 13-21 are earnestly requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 240042052403. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: May 10, 2001 By: 

Peng Chen
Registration No. 43,543

Morrison & Foerster LLP
3811 Valley Centre Drive
Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5147
Facsimile: (858) 720-5125